



DEPARTMENT OF HEALTH & HUMAN SERVICES

HID 613
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-156/S-038, S-039

Monarch Pharmaceuticals
Attention: Thomas K. Rogers III
Vice President Regulatory Affairs
501 Fifth Street
Bristol, TN 37620

FEB 3 1999

Dear Mr. Rogers:

Please refer to your supplemental new drug applications dated November 6, 1996 (S-038), and January 9, 1997 (S-039), submitted under the Federal Food, Drug, and Cosmetic Act for Chloromycetin (chloramphenicol ophthalmic ointment, USP) Ophthalmic Ointment, 1%. We also refer to our approvable letters dated June 15, 1997 (S-038) and June 29, 1997 (S-039).

We acknowledge receipt of your submissions dated June 25, 1997, and December 18, 1998 (two).

Supplemental application S-038 provides for revisions to the package insert.

Supplemental application S-039 provides for a change in the diluent gas for ethylene oxide sterilization.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling submitted December 18, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

We request that at the next printing or within six months, whichever comes first, the generic name on the tube and carton labels be revised so that it appears in all lower case letters, as "chloramphenicol ophthalmic ointment, USP."

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-156/S-038, S-039." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 2/3/99

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Chloromycetin Ophthalmic Ointment, 1 %

(chloramphenicol ophthalmic ointment, USP)

307G010

224



WARNING

Bone marrow hypoplasia including aplastic anemia and death has been reported following topical application of chloramphenicol. Chloramphenicol should not be used when less potentially dangerous agents would be expected to provide effective treatment.

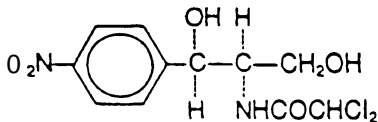
DESCRIPTION

Chloromycetin Ophthalmic Ointment 1% is a topical anti-infective product for ophthalmic use.

Each gram of Chloromycetin Ophthalmic Ointment 1% contains 10 mg of chloramphenicol in a special base of liquid petrolatum and polyethylene. This sterile ointment contains no preservatives.

The chemical names for chloramphenicol are:

- (1) Acetamide, 2,2-dichloro-N-[2-hydroxy-1 -(hydroxymethyl)-2-(4-nitrophenyl) ethyl]-, and
 - (2) D-threo-(-)-2,2,Dichloro-N-[B-hydroxy-a-(hydroxymethyl)-p-nitrophenylethyl] acetamide.
- Chloramphenicol has the following empirical and structural formulas:



Mol Wt 323.13

CLINICAL PHARMACOLOGY

Microbiology

Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae*. It is primarily bacteriostatic and acts by inhibition of protein synthesis by interfering with the transfer of activated amino acids from soluble RNA to ribosomes.

Chloramphenicol has been shown to be active against the following organisms:

Aerobic gram-positive microorganisms:

Staphylococcus aureus

Streptococcus, including *Streptococcus pneumoniae*

Aerobic gram-negative microorganisms:

Enterobacter sp.

Escherichia coli

Haemophilus influenzae

Klebsiella sp.

Moraxella lucunata (Morax-Axenfeld bacillus)

Neisseria sp.

This product does not provide adequate coverage against *Pseudomonas aeruginosa* or *Serratia marcescens*. Bacteriological studies should be performed to determine the causative organisms and their susceptibilities to chloramphenicol.

INDICATIONS AND USAGE

Chloramphenicol should be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. (see Boxed Warning)

Chloromycetin Ophthalmic Ointment 1% (chloramphenicol ophthalmic ointment, USP) is indicated for the treatment of surface ocular infections involving the conjunctiva and/or cornea caused by chloramphenicol-susceptible organisms. (see Clinical Pharmacology Microbiology)

CONTRAINDICATIONS

This product is contraindicated in persons sensitive to any of its components.

WARNINGS**SEE BOXED WARNING**

Occasionally one sees hematopoietic toxicity with the use of systemic chloramphenicol, and rarely with topical administration. This type of blood dyscrasia is generally a dose-related toxic effect on bone marrow and is usually reversible on cessation of the drug. Rare cases of aplastic anemia have been reported with prolonged (months to years) or frequent intermittent (over months and years) use of topical chloramphenicol.

Ophthalmic ointments may retard corneal wound healing.

PRECAUTIONS**General**

The prolonged use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms including fungi. If new infections appear during medication or clinical improvement is not observed within 1 week the drug should be discontinued and appropriate measures should be taken.

Chloromycetin Ophthalmic Ointment, 1%

(chloramphenicol ophthalmic ointment USP)

Information for patients: Do not touch bottle tip to any surface as this may contaminate the solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted in animals or in humans to evaluate the carcinogenic potential or effects on fertility with chloramphenicol. However, there is some clinical evidence that aplastic anemia due to chloramphenicol may be associated with subsequent development of leukemia

Pregnancy

Pregnancy Category C - Chloramphenicol has been shown to be embryocidal and teratogenic in rat, mouse, rabbit and chicken embryos/fetuses (see below). There are no adequate and well-controlled studies in pregnant women. Chloramphenicol has been shown to cross the placental barrier, but is not known whether chloramphenicol can cause fetal harm when administered to a pregnant woman. Chloramphenicol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryotoxic effects: Significantly lower numbers of live fetuses and an increase in the number of early embryonic resorptions occurred after pregnant rats were treated orally with 500 mg/kg (equivalent to 3750 times the recommended maximum daily adult topical ophthalmic dose) from days 5 to 15 of their pregnancy. Similar findings were seen with groups receiving higher oral doses (1000 mg/kg or 2000 mg/kg) at various dosing intervals. Female mice receiving 1000 mg/kg orally from days 6 to 12 of their pregnancy showed a significant increase in the number of resorptions. Female rabbits receiving the same oral dosing (1000 mg/kg from days 8 to 11) had an increase in the number of resorptions of embryos without placentation. Chloramphenicol (2.5 mg) injected into chicken eggs resulted in a 20% embryo mortality rate one day after administration, which increased to 100% embryo mortality on the 11th day of incubation.

Teratogenicity: When given to female rats orally at 2000 mg/kg from days 6 to 8 of pregnancy, 36% of the fetuses exhibited either an omphalocele or an umbilical hernia, with costal fusions. Fetuses of the rats treated with 1000 mg/kg orally from days 7 to 12 of pregnancy or 2000 mg/kg from days 11 to 13, and of mice treated with 1000 mg/kg from days 6 to 12, had a higher incidence of missing ossification of the phalangeal nuclei of the forelegs and hindlegs and of the 5th sternum. This correlated with a decrease in the average weight of the fetuses. Rabbit fetuses displayed more frequent absence of the phalangeal nuclei of the forelegs than control when pregnant rabbits received 500 mg/kg orally on days 6 to 15 of pregnancy. More frequent missing ossification of the phalangeal nuclei of the forelegs and hindlegs and an increase in the number of unevenly ossified vertebrae was seen in the fetuses of rabbits when pregnant females were given 1000 mg/kg from days 6 to 9 of pregnancy. Teratogenic effects of chloramphenicol (0.5 mg) when injected into chicken eggs, included malformations of the beak, eyes and legs.

Nursing Mothers

Chloramphenicol appears in human milk following oral administration of the drug. Systemic absorption of chloramphenicol may occur when applied topically. Because of the potential serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy in pediatric patients below 1 year of age have not been established.

ADVERSE REACTIONS

Exact incidence figures are not available since no denominator of treated patients is available.

The most serious reaction following prolonged or frequent intermittent use of topical chloramphenicol is bone marrow aplasia.

The most frequently reported adverse reactions have been burning, stinging and ocular irritation. Blood dyscrasias, allergic or inflammatory reactions due to individual hypersensitivity, angioneurotic edema, urticaria, vesicular and maculopapular dermatitis have also been reported (See Warnings and Box Warning).

DOSAGE AND ADMINISTRATION

A small amount of ointment placed in the lower conjunctival sac every three hours, or more frequently if deemed advisable by the prescribing physician. Treatment should be continued for approximately 7 days but should not be continued for more than three weeks without re-evaluation by the prescribing physician.

HOW SUPPLIED

NDC 61570-307-01 Chloromycetin Ophthalmic Ointment, 1% (chloramphenicol ophthalmic ointment USP) is supplied sterile, in ophthalmic ointment tubes of 3.5 grams.

Store below 30°C (86°F).

Rx only.

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured by: Parkedale Pharmaceuticals, Inc., Rochester, MI 48307



307GOIO
Rev. 10/98
224